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First Named Inventor	Gregg B. Morin, et al.
Art Unit	1632
Examiner Name	Paul Thomas Dowell, Ph.D.
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ENCLOSURES *(Check all that apply)*

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Remarks

Declaration under 37 CFR § 1.132 by Calvin B. Harley Ph.D. (9 pages)
(References in support of Declaration filed in IDS under separate cover)

Last page marker.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	Geron Corporation		
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Printed name	J. Michael Schiff		
Date	Sept 25/06	Reg. No.	40,253

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors: Gregg Morin et al.

Filing Date: July 11, 2000

Serial No: 09/615,039

Docket: 019/251c

Title: ONCOLYTIC VIRUS THAT REPLICATES IN CELLS EXPRESSING TELOMERASE REVERSE TRANSCRIPTASE

Art Unit: 1632

Examiner: Paul Thomas Dowell, Ph.D.

DECLARATION UNDER 37 CFR § 1.132

CALVIN B. HARLEY, Ph.D.

Commissioner for Patents
Alexandria VA 22313

Dear Sir:

I, CALVIN HARLEY, do hereby declare as follows:

I am the Chief Scientific Officer at Geron Corporation. I have been conducting research on telomere biology and biochemistry for over 15 years, and have authored over 40 research papers and reviews on the subject. I am co-inventor on about 23 issued U.S. Patents covering telomerase compositions, assays, and inhibitors.

My role at Geron is to oversee the company's entire scientific research program, including the development of human telomerase reverse transcriptase (TERT) for human therapy. Geron has a collaboration with Cell Genesys to develop an oncolytic adenovirus driven by the TERT promoter for the treatment of cancer [1,2].

Non-obviousness of this invention

I understand the Examiner has questioned whether the invention claimed in this patent application would have been obvious to someone skilled in this technological area at the time the priority application was filed on February 4, 1999. In particular, the Examiner refers to the following references:

- U.S. Patent 5,998,205 (Hallenbeck et al.), which generally describes replication conditional adenovirus vectors, and U.S. Patent 5,278,379 (Martuza et al.), which generally describes replication conditional herpes vectors;
- The articles by Kim et al. [3] and Kanazawa et al. [4], which report that TERT is preferentially expressed in cancer cell lines; and
- The article by Takakura et al. [5] or issued U.S. Patent 6,610,839 (Morin et al.), which provide the promoter sequence for human TERT.

As I understand it, the Examiner suggests that upon learning about replication conditional vectors from the Hallenbeck and Martuza patents, the reader would be guided by the Kim and Kanazawa references to use the TERT promoter in place of the promoters used by Hallenbeck and Martuza.

In my expert opinion, someone knowledgeable in telomere biology would reasonably doubt whether the hTERT promoter would be suitable for use in an oncolytic virus in view of what was then known about TERT expression in essential stem cells. This could easily guide someone away from using the hTERT promoter, in favor of any one of a number of other promoters known at the time to cause differential expression in cancer cells.

Alternative promoters

At the time the priority application was filed in 1999, extensive work had been done to identify markers that are expressed at high levels in human cancers. Carcinoembryonic antigen (CEA) and other markers were described in the 1960's, foreshadowing an era of extensive research and discovery for tumor-specific and tumor-associated markers (reviewed in ref. 6). Such markers have been seen as possible targets for treatment by way of cancer vaccines [7], or as a way of causing gene vectors to be expressed preferentially in cancer cells [8,9,10].

For example, Cooper [8], a 1996 reference, reviews the potential for targeted gene therapy, listing over 20 different promoters, each drawn from previous articles. Dachs et al. [9], a 1997 reference, discusses the use of particular transcription control elements for α-fetoprotein, DF3 (MUC1), albumin, tyrosinase, von Willebrand factor (wWF), glial fibrillary acidic protein promoter (GFAP), myelin basic protein (MBP), myelin proteolipid protein (PLP), osteocalcin, CEA, HER-2/neu (erb B2), Myc-Max, the early growth response gene Egr-1, tissue plasminogen activator (tPA), glucose regulated protein GRP78/BiP, hypoxia inducible factor HIF-1, and phosphoglycerate kinase-1. Patterson et al. [10], a 1999 reference, lists 12 different tissue specific, tumor specific, or radiation inducible promoters suitable for treating breast cancer.

The Hallenbeck and Martuza patents referred to by the Examiner also provide a long list of alternative promoters for use in oncolytic viruses.

The working example in the Hallenbeck patent use the promoter for α-fetoprotein (Example 1). Recommended alternatives are mostly selected from the list given in the Dachs article: namely, transcription regulatory sequences for carcinoembryonic antigen (CEA), the DF3 mucin (MUC1), Erb-B2, surfactant, and tyrosinase. The Martuza patent provides an extensive list of tissue- and tumor-specific promoter which it say scan be used in the vectors of their invention. Table 1 lists 56 such promoters; Table 2 lists about 24 such promoters. Each table refers to cancer types suitable for treatment, and references where more information about the promoters referred to can be found.

Thus, someone reading the Hallenbeck and Martuza patents and other published documents would have a large number of promoters to select from that are listed within the references. They would also be aware of a wide variety of other promoters that would be good candidates for driving an oncolytic virus.

Potential risks of using the TERT promoter

Even if it occurred to someone reading the Hallenbeck or Martuza patents to consider using the TERT promoter, it is my opinion that they may have been more inclined to use other alternatives, in view of what was known about the pattern of telomerase expression at the time the priority application was filed in 1999.

The genetically programmed role of telomerase is not to create tumors, but to increase replicative capacity of certain normal cells needed by the human organism. TERT is not expressed in most normal human cells. Consequently, they can replicate through typically 30 to 100 cell divisions (the Hayflick limit), because telomere ends of chromosomes shorten each time the cell divides, until the cell enters replicative senescence or crisis.

However, it was known in 1999 that the germline cells and certain somatic stem or progenitor cells from highly proliferative tissues *do* express telomerase activity (and hence both hTR and TERT), apparently conferring an increased replication capacity to these cells (reviewed in ref. 11). Amongst normal cells that express TERT are germline cells [12,13,14], activated lymphocytes [13,15,16], and cells from proliferative tissues such as bone marrow [14,17] hematopoietic progenitors [18], spleen [14], colonic crypt epithelial cells [19], breast epithelium [20], and the stratum basale of the skin [20].

Accordingly, someone working with oncolytic viruses would be concerned that a vector driven by the TERT promoter has the potential to eliminate too many essential stem cells. If so, the following side effects could occur:

- Generalized growth defects
- Depletion of hematopoietic stem cells in the bone marrow, leading to pancytopenia and marrow failure;
- Depletion of crypt epithelial cells, leading to diarrhea and malnutrition;
- Depletion of skin and hair follicle stem cells, leading to alopecia (hair loss) and poor wound healing; and
- Impaired ability of the immune system to prevent opportunistic infection.

Furthermore, since TERT is expressed in mouse hepatocytes [21] and since adenovirus is hepatotropic, it could be predicted that an oncolytic virus based on adenovirus would cause hepatotoxicity (leading to an elevation in liver enzymes in the circulation), and toxicity of the spleen.

Demonstrations that a TERT-driven oncolytic virus is both safe and effective

This patent application provides an illustration of this invention in which an adenovirus was constructed in which the E1A adenovirus gene was placed under control of the promoter for human TERT. The data show that the TERT oncovirus replicated killed a panel of six different cancer cell lines, but not three long-lived mortal cell lines (Example 10, Figure 4, Table 2).

Accompanying this Declaration is our article presenting follow-on data obtained using the same oncolytic virus (Irving et al., ref. 1). Administration of the virus into nude mice bearing human liver or prostate tumor xenografts produced significant tumor reduction, and in some cases, resulted in complete tumor regression (Figure 4). This correlated with E1A gene expression *in vivo* (Figure 5). Importantly, there was no evidence of toxicity to the liver, even though another construct driven by the CMV promoter caused hepatocyte vacuolation and cellular necrosis (Figure 6). Although the human TERT promoter is known to drive expression in mouse stem cells [22], there was no evidence for any of the stem cell related side effects predicted above. Thus, the relative proliferation rate in cancer cells compared with stem cells is high enough to provide genuine therapeutic value.

Subsequent studies by other laboratories using TERT driven oncolytic viruses confirm and amplify these results:

- Lanson et al. [23] studied an oncolytic virus in which the E1A gene was controlled by the human TERT promoter. They reported that a *single injection* of the oncolytic virus into preexisting HT-1080 fibrosarcoma tumors in nude mice efficiently suppressed tumor growth.
- Huang et al. [24] studied a similar construct, showing that replication was severely attenuated in TERT-negative cells, but that it replicated almost as efficiently as wild-type adenovirus in TERT-positive cells. In vivo replication after local administration into a xenograft model of human hepatocellular carcinoma in nude mice resulted in increased titers in tumor extracts by *several orders of magnitude* within 3 days of injection, correlating with inhibition of tumor growth and tumor cell necrosis. *There was no evidence of hepatotoxicity.*
- Kuppuswamy et al. [25] found that an oncolytic adenovirus vector with the TERT promoter driving E4 reduced the number and size of A549 human lung cancer cell nodules in a disseminated lung tumor model (a model for *metastatic disease*). Different doses of the construct showed *minimal liver toxicity.*

- Wirth et al. [26] found that a single dose of a TERT-depending conditionally replicating adenovirus led to significant inhibition of growth of Huh7 hepatoma xenografts. *The TERT mediated oncolysis was more efficient than treatment with ONYX-015,* an extensively studied vector that replicates selectively in p53 mutated cells [27].

<u>Summary</u>

In my view, someone reading the Hallenbeck and Martuza patents back in 1999 would not necessarily conclude that the TERT promoter would be safe and efficacious in an oncolytic virus. Many other promoters were known and extensively studied in other laboratories that would be suitable. The potential risks of using TERT could make the other alternatives seem more attractive.

Nevertheless, this patent disclosure and the subsequent studies show that the oncovirus of this invention is both safe and effective. Although TERT is expressed in stem cells, oncovirus vectors driven by the TERT promoter are sufficiently tumor-selective so as to be therapeutic without substantial side effects . Even a single low dose may result in significant inhibition of tumor growth in preclinical studies. The virus is effective in models for metastatic disease, and is superior to the ONYX-015 vector for which there is evidence of efficacy in human clinical trials.

I hereby declare that all statements made in this Declaration of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

2006.09.21
Date

Calvin B. Harley
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Menlo Park, CA

PATENT
09/615,039
Docket 019/251c

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